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# Guidance for Industry Controlled Correspondence Related to Generic Drug Development

## ***DRAFT GUIDANCE***

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For questions regarding this draft document contact (CDER) Maryll Toufanian at 240-402-7944.

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)**

**August 2014  
Generics**

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# Guidance for Industry Controlled Correspondence Related to Generic Drug Development

*Additional copies are available from:*

*Office of Communications*

*Division of Drug Information, WO51, Room 2201*

*Center for Drug Evaluation and Research*

*Food and Drug Administration*

*10903 New Hampshire Ave., Silver Spring, MD 20993*

*Phone: 301-796-3400; Fax: 301-847-8714*

*druginfo@fda.hhs.gov*

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)**

**August 2014  
Generics**

*Contains Nonbinding Recommendations*

*Draft — Not for Implementation*

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**Guidance for Industry<sup>1</sup>**  
**Controlled Correspondence Related to**  
**Generic Drug Development**

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

**I. INTRODUCTION**

This guidance provides information regarding the process by which generic drug manufacturers and related industry can submit correspondence to the Food and Drug Administration (FDA or the Agency) requesting information related to generic drug development. This guidance also describes FDA's process for providing communications related to such correspondence. FDA is issuing this draft guidance as part of the Agency's implementation of the Generic Drug User Fee Amendments of 2012 (Public Law 112-144, Title III), commonly referred to as GDUFA.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

**II. BACKGROUND**

On July 9, 2012, GDUFA was signed into law by the President.<sup>2</sup> GDUFA is designed to speed the delivery of safe and effective generic drugs to the public and to reduce costs to industry. The law is based on an agreement negotiated by FDA and representatives of the generic drug industry to address a growing number of regulatory challenges. GDUFA reflects input received during an open process that included regular public meetings, posting of meeting minutes, and consideration of comments from a public docket. Agreed-upon recommendations were sent to

<sup>1</sup> This guidance has been prepared by the Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

<sup>2</sup> On October 5, 2012, the President signed into law the FDA User Fee Corrections Act of 2012 (Public Law 112-193). This act amends GDUFA so that due dates for GDUFA user fees in fiscal year 2013 are not dependent on enactment of an appropriations act.

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Congress, and Congress held hearings on GDUFA that included testimony from FDA, the generic drug industry, and other interested parties.

GDUFA requires that FDA and human generic drug manufacturers alike must meet certain requirements and commitments. Under GDUFA, FDA has agreed to specific program enhancements and performance goals as set forth in the GDUFA Commitment Letter<sup>3</sup> that accompanies the legislation. The GDUFA Commitment Letter included detail on FDA's commitment to respond to questions submitted as "controlled correspondence" within certain time frames. Specifically, the Agency agreed that:

- FDA will respond to 70 percent of controlled correspondence in 4 months from date of submission in fiscal year (FY) 2015.
- FDA will respond to 70 percent of controlled correspondence in 2 months from date of submission in FY 2016.
- FDA will respond to 90 percent of controlled correspondence in 2 months from date of submission in FY 2017.
- If the controlled correspondence requires input from the clinical division, one additional month will be added to the goals outlined above.<sup>4</sup>

The GDUFA Commitment Letter described *controlled correspondence* as follows:

FDA's Office of Generic Drugs provides assistance to pharmaceutical firms and related industry regarding a variety of questions posed as "controlled documents." See [\[http://www.fda.gov/AboutFDA/CentersOffices/officeofmedicalproductsandtobacco/CDER/ucm120610.htm\]](http://www.fda.gov/AboutFDA/CentersOffices/officeofmedicalproductsandtobacco/CDER/ucm120610.htm). Controlled correspondence does not include citizen petitions, petitions for reconsideration, or requests for stay.<sup>5</sup>

This guidance provides additional detail and recommendations concerning:

- what inquiries FDA considers as controlled correspondence for the purposes of meeting the Agency's GDUFA commitment;
- what information requestors can include in a controlled correspondence to facilitate FDA's consideration of and response to a controlled correspondence; and
- what information FDA will provide in its communications to requestors that have submitted controlled correspondence.

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<sup>3</sup> See Generic Drug User Fee Act Program Performance Goals and Procedures (GDUFA Commitment Letter) for fiscal years 2013 through 2017, available at <http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf>.

<sup>4</sup> GDUFA Commitment Letter at 12. Any controlled correspondence submitted before October 1, 2014, does not fall under the time frames and goal dates identified in the GDUFA Commitment Letter. Notwithstanding, FDA intends to respond to those controlled correspondence as expeditiously as is practicable.

<sup>5</sup> GDUFA Commitment Letter at 15. We note that the Web page link quoted in the definition above has been updated to reflect the current link, because the link provided in the GDUFA Commitment Letter is no longer accessible.

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Many of the recommendations in this guidance incorporate FDA’s historical practices in responding to controlled correspondence that were detailed on the Web page cited in the GDUFA Commitment Letter referenced above.<sup>6</sup>

### **III. CONTROLLED CORRESPONDENCE**

#### **A. Definition of *Controlled Correspondence***

As detailed in the GDUFA Commitment Letter, the aims of the generic drug user fee program include (1) ensuring the safety of generic drug products; (2) enhancing access by expediting the availability of these products; and (3) enhancing transparency by, among other things, improving FDA’s communications and feedback with industry to expedite product access. Each of these goals is designed to directly benefit the public health. FDA and industry identified controlled correspondence in the GDUFA Commitment Letter as one mechanism to support these aims. The GDUFA Commitment Letter did not provide a precise definition of *controlled correspondence*, however. The Agency thus has determined that the term should be further defined in a manner that best supports these principles. Accordingly, FDA defines *controlled correspondence* for the purposes of GDUFA as follows:

**A correspondence submitted to the Agency, by or on behalf of a generic drug manufacturer or related industry, requesting information on a specific element of generic drug product development.**

We believe that this definition encompasses the broad spectrum of issues that can arise as generic drug manufacturers and related industry begin drug development that can benefit from targeted Agency consideration and, at the same time, helps to ensure that Agency resources supported by user fees are focused on facilitating and expediting development of generic drug products. Examples of the numerous topics that fall within the definition are described in sections IV.C-D, below.

#### **B. Additional Guidance on Inquiries Inside the Scope of Controlled Correspondence**

##### **1. *Controlled Correspondence Concerning Issues Raised in a Pending Citizen Petition, Petition for Reconsideration, or Request for Stay***

If a controlled correspondence is submitted that raises an issue that is the same as or related to an issue or question that is the subject of one or more pending citizen petitions, petitions for reconsideration, or requests for a stay, the goal dates set forth in the GDUFA Commitment Letter for controlled correspondence will apply from the date FDA issues responses to the pending petitions.<sup>7</sup> Likewise, if a citizen petition, petition for reconsideration, or request for stay is submitted that raises an issue that is the same as or related to an issue or question in a pending controlled correspondence, the goal date for that controlled correspondence will apply from the

<sup>6</sup> See Recommendations for Improving Submissions of a “Controlled Correspondence” to the Office of Generic Drugs, available at

<http://www.fda.gov/AboutFDA/CentersOffices/officeofmedicalproductsandtobacco/CDER/ucm120610.htm>.

<sup>7</sup> As set forth in the GDUFA Commitment Letter, *controlled correspondence* do not include citizen petitions, petitions for reconsideration, or requests for stay, even if they raise issues related to generic drug development (GDUFA Commitment Letter at 12).

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date FDA issues a response to the related citizen petition, petition for reconsideration, or stay request. For example, if a controlled correspondence is submitted in FY 2015 that relates to an issue in a pending petition, and the Agency responds in FY 2016 to that petition, the 4-month goal date for FY 2015, the year in which the controlled correspondence was submitted, will apply to the controlled correspondence from the 2016 date that the petition is answered.

### ***2. Requests Related to Matters Still Under Consideration by the Agency***

FDA occasionally receives requests for information on issues that the Agency is considering, but for which no regulatory decision has been made. For example, FDA might receive a controlled correspondence seeking information on specific approval requirements for an abbreviated new drug application (ANDA) for a complex drug product for which FDA is still considering the scientific standards for approval. For such questions that call for developing a new policy, FDA will respond to the controlled correspondence to notify the requestor that such a policy is under development, but that the Agency cannot provide information at that time because the matter is still under consideration. The Agency will consider this response to close the controlled correspondence, and it will not provide additional direct communications to an inquirer on the matter. We note that these types of issues are often the subject of Agency guidance.

## **C. Guidance on Inquiries Outside the Scope of Controlled Correspondence**

### ***1. Exceptions to the Definition of Controlled Correspondence***

Historically, three types of inquiries fall within the above definition of *controlled correspondence* that FDA has treated differently than other inquiries on generic drug development: (1) requests for recommendations on the appropriate design of bioequivalence (BE) studies for a specific drug product (BE guidance requests), (2) requests for review of BE clinical protocols (clinical protocol requests), and (3) requests for meetings to discuss generic drug development prior to ANDA submission (pre-ANDA meeting requests). FDA will continue to respond to these inquiries consistent with its current practices, and to exclude these inquiries from the goal dates in the GDUFA Commitment Letter, as described below.

First, FDA will continue to address BE guidance requests consistent with the public process described in the Agency's guidance for industry on *Bioequivalence Recommendations for Specific Products*.<sup>8</sup> Under this approach, FDA publishes BE recommendations in product-specific guidances, the availability of which are announced in the *Federal Register* and are open to comment for a designated time period. Before establishing this public process, FDA responded to requests for guidance on BE studies on an individual basis. Under that process, information about BE studies was only being provided to those parties specifically requesting such information, and it created a significant burden on those FDA individuals responsible for reviewing both the BE data in ANDAs and requests for recommendations on BE methodologies. The product-specific guidance process enhances transparency, provides a mechanism for public comment on recommended BE studies, and provides for more efficient use of Agency resources.

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<sup>8</sup> We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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With this public process, FDA can be proactive in developing and publishing guidance for new drug products without waiting for inquiries on BE methodologies from individual requestors. As contemplated in the GDUFA Commitment Letter, this effort will also include guidance development resulting from the regulatory science initiatives funded by generic drug user fees. FDA anticipates that this process will continue to expedite the availability of BE methodologies to generic drug developers. This process involves time frames that differ from the goal dates for controlled correspondence, however, and the Agency has determined that it would not be appropriate to circumvent this public process by responding to individual requestors in order to meet the GDUFA goal dates for controlled correspondence. Although BE guidance requests will not be treated as a controlled correspondence for the purposes of the GDUFA goal dates, we recommend that requestors continue to submit BE guidance requests for proposed products to [GenericDrugs@fda.hhs.gov](mailto:GenericDrugs@fda.hhs.gov) so that the Agency can continue to consider these requests in prioritizing BE guidance development.<sup>9</sup>

Second, FDA will continue to exclude clinical protocol requests from controlled correspondence, and the related goal dates. These are requests for review of clinical protocols for in vivo BE studies with pharmacokinetic, pharmacodynamic, or clinical end-point studies conducted in support of demonstrating BE for a proposed generic product. Historically, FDA has not considered such requests as controlled correspondence, because these requests are more time- and resource-intensive than other requests and often call for consultation with multiple disciplines within OGD, as well as with other offices in CDER. Notwithstanding exclusion from the category of controlled correspondence for the purposes of GDUFA goal dates, we recommend that parties continue to submit clinical protocol requests to [GenericDrugs@fda.hhs.gov](mailto:GenericDrugs@fda.hhs.gov) so that the requests can be promptly reviewed by the correct discipline. FDA will respond to clinical protocol requests as expeditiously as practicable.

Third, FDA will not treat pre-ANDA meeting requests as controlled correspondence with related GDUFA goal dates, because such requests serve a different purpose than controlled correspondence and should include different information from an inquirer. The purpose of the controlled correspondence process is to provide a mechanism for a direct inquiry on FDA's position with respect to a particular element of generic drug development, and for the Agency's direct response. The purpose of a pre-ANDA meeting request, by contrast, is to seek a dialogue with the Agency on a particular matter for which the controlled correspondence process is not suitable. Similarly, materials and information submitted with a controlled correspondence should provide the Agency with the relevant information on which to base its considerations, while the materials submitted in support of a meeting request should help the Agency determine whether a meeting is appropriate. Accordingly, we will treat these meeting requests separately. Like BE guidance requests and clinical protocol requests, however, we recommend that parties continue to submit pre-ANDA meeting requests to [GenericDrugs@fda.hhs.gov](mailto:GenericDrugs@fda.hhs.gov) so that these requests can be promptly considered by the Agency.

### ***2. Topics Outside the Scope of Controlled Correspondence***

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<sup>9</sup> We encourage requests for consideration of BE methods that modify or deviate from those proposed for a specific product to be submitted to the public docket of the particular product-specific BE guidance. As an alternative, the inquirer can submit a controlled correspondence. In addition, if a requestor wants clarification on a BE study recommended in a specific draft guidance, the requestor can submit an inquiry as a controlled correspondence.



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This section provides additional guidance on what types of inquiries or topics do not fall within the definition of *controlled correspondence* described above. First, the Agency considers any question related to a pending ANDA a review issue. Such inquiries will not be treated as controlled correspondence and should be submitted only to the ANDA so they can be included as part of the full administrative record for that application.<sup>10</sup>

Second, inquiries that are submitted to FDA that are not directly related to generic drug development will not be considered controlled correspondence for the purposes of GDUFA. For example, inquiries requesting information on the administrative practices of OGD, or on development of generic products for which there has never been a U.S.-approved reference listed drug (RLD), will not be considered controlled correspondence.

Third, as reflected in the definition of *controlled correspondence*, FDA expects that controlled correspondence will contain inquiries on *a specific element* of generic drug development, and not general questions related to product planning. Consistent with FDA's past practices, general, open-ended, or insufficiently detailed questions related to product development are not the appropriate subject of these inquiries. For example, an inquiry seeking information on general approval standards for a particular product is not the appropriate subject of a controlled correspondence for the purposes of GDUFA. FDA provides information to stakeholders on its approval standards and the general submission recommendations through FDA regulations and guidances. The controlled correspondence process is intended to facilitate, and not supplant, the generic drug developmental endeavor.

### ***3. Entities Outside the Scope of Controlled Correspondence***

The controlled correspondence process, historically (and under the definition above), is available to generic drug manufacturers and related industry (e.g., contract research organizations conducting bioanalytical or BE clinical trials) or their representatives, because this mechanism exists to facilitate generic drug development. Inquiries related to generic drugs submitted by other parties (for example, private citizens, financial firms, or public advocacy groups that are not directly involved in developing generic drug products) should be directed to CDER's Division of Drug Information.<sup>11</sup>

## **IV. SUBMITTING A CONTROLLED CORRESPONDENCE**

### **A. How to Submit a Controlled Correspondence**

Consistent with the agreement from industry described in the GDUFA Commitment Letter, requestors seeking FDA's response to a controlled correspondence by the goal dates articulated in the GDUFA Commitment Letter (and listed above) should submit the correspondence electronically, via email to [GenericDrugs@fda.hhs.gov](mailto:GenericDrugs@fda.hhs.gov).<sup>12</sup> This will facilitate prompt

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<sup>10</sup> We note that the Agency will consider a request for information in a controlled correspondence regarding development of a new strength for a product for which there is a pending ANDA for other strengths.

<sup>11</sup> See contact information for the Division of Drug Information on the second title page of this guidance.

<sup>12</sup> The GDUFA Commitment Letter provides that "[b]ecause certain databases to implement this program will need to be built, and existing systems need to be expanded or modified, industry will submit necessary information in electronic format to FDA using appropriate standards to be specified by the [A]gency or as specified in statute."

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consideration of and response to the controlled correspondence by the appropriate discipline. The email should be sent from a corporate email address. For these reasons, we do not intend to consider emails generated from general, personal accounts as controlled correspondence.

**FDA strongly discourages submitting controlled correspondence to individual FDA employees, and submitting additional copies of a controlled correspondence in paper form, by courier, or by facsimile.** As described in section V below, FDA intends to provide requestors notification via email on the status of a request soon after it is submitted, which should provide a requestor adequate assurance that the Agency has received the communication, and either state that it is considering the request as a controlled correspondence, or provide the basis for not responding to an inquiry as a controlled correspondence, as described in this guidance.

### **B. Content of a Controlled Correspondence**

FDA recommends the following information be included at the beginning of a controlled correspondence:

- Name, title, address, phone number, and entity (e.g., corporate affiliation) of the person submitting the controlled correspondence.

FDA is only able to provide a response to the U.S. agent or representative of a foreign company, similar to FDA practice when an ANDA is submitted.

- An email address to which a response to the controlled correspondence can be sent.

We note that a requestor (or its U.S. agent) may apply for a secure email pathway by contacting [secureemail@fda.hhs.gov](mailto:secureemail@fda.hhs.gov).

- The FDA-assigned control number and submission date of any previous, related controlled correspondence, if applicable, as well as a copy of that previous controlled correspondence and FDA's response, if any.
- Relevant RLD(s), as applicable, including application number, proprietary (brand) name, manufacturer, active ingredient, dosage form, and strength(s).
- A concise statement of the inquiry for which the controlled correspondence is being submitted.
- A recommendation of the appropriate review discipline to review the controlled correspondence.

General information regarding review disciplines is provided in section IV.D, below.

- Relevant prior research and supporting materials.

FDA recommends that a requestor include the pertinent prior research and supporting information on the specific element of generic drug development for which information is

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(GDUFA Commitment Letter at 9). In addition, the letter provides that “[r]eview metric goals [...] only apply to submissions made electronically, following the eCTD format in effect at the date of submission” (id. at 7).

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sought in the controlled correspondence. If FDA determines, upon receipt of a controlled correspondence, that the correspondence lacks sufficient information to consider the inquiry, it will notify the requestor of this deficiency and close the controlled correspondence. If FDA determines, during the substantive review of the inquiry, that the inquiry lacks sufficient information, it can either close the control at that time or contact the requestor for additional information. If the Agency decides to close the control, it will notify the requestor of that decision. If FDA contacts the requestor for additional information, the goal-date period will be extended by the amount of time that the Agency's request for additional information is outstanding with the requestor.

### **C. Additional Recommendations on the Content of Specific Types of Controlled Correspondence Inquiries**

This section provides additional recommendations for the content of specific types of inquiries submitted as controlled correspondence.

#### ***1. Requests Related to Inactive Ingredients***

The Agency often receives requests for information pertaining to whether particular inactive ingredients that are higher than the maximum levels listed in the Agency's Inactive Ingredient Database can be used in a generic drug product. FDA recommends that a requestor submit no more than three inactive ingredients per request for such assessment.

#### ***2. Requests for Q1/Q2 Formulation Assessment***

For certain types of products, FDA's regulations require that proposed products be qualitatively (Q1) and quantitatively (Q2) the same as the RLD with respect to inactive ingredients.<sup>13</sup> In addition, FDA sometimes recommends certain BE studies for drug products that are Q1/Q2 with respect to the RLD. For controlled correspondence seeking review of proposed Q1/Q2 formulations, we recommend that the following information be included in the controlled correspondence, which can also be found in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (commonly referred to as the Orange Book):

- the relevant RLD sponsor
- application number
- proprietary name
- active ingredient
- dosage form
- route of administration
- RLD approval date
- whether the product is prescription, over-the-counter, or in the "Discontinued" section of the Orange Book, which lists drug products that have been withdrawn from the market.

FDA recommends that no more than three proposed Q1/Q2 formulations of a single drug product be submitted in one controlled correspondence. Adequate details should be included in the formulation descriptions, including salt and hydration forms of the active ingredients and excipients.

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<sup>13</sup> See, e.g., 21 CFR 314.94(a)(9)(iii).

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If a requestor is seeking formulation assessment for multiple drug products, FDA recommends that each request be submitted in a separate controlled correspondence. Thus, a requestor should not seek Q1/Q2 formulation assessment for generic products with different RLDs in a single controlled correspondence. This also includes separate formulation assessment requests for drug products with multiple strengths, because each strength is a separate drug product. Consistent with the Agency's past practice, FDA does not intend to review proposed formulations that are not required or FDA-recommended to be Q1/Q2 to the RLD.

### ***3. Requests Requiring Review by More than One Discipline***

If a requestor seeks information related to separate elements of generic drug product development (e.g., information on proposed formulation and proposed product labeling), FDA recommends that the requestor submit separate requests regarding the product. This will facilitate timely review and response.

## **D. Controlled Correspondence Review Disciplines**

This section provides additional information on the different disciplines that might review and respond to a controlled correspondence. In addition, this section provides examples of the types of inquiries a discipline might review. The Agency anticipates that this information will assist requestors in recommending the appropriate discipline to review a particular controlled correspondence, as suggested above. These descriptions are not intended to be exhaustive, and FDA has the discretion to determine which discipline should review and respond to a controlled correspondence.

- **Division of Chemistry**

FDA anticipates that the Division of Chemistry will review, for example, correspondence containing inquiries regarding chemistry, manufacturing, and controls of generic drugs (with the exception of inquiries related to microbiology, which is discussed below).

- **Office of Bioequivalence**

FDA anticipates that the Office of Bioequivalence will review correspondence containing inquiries during the planning of BE studies. Within the Office of Bioequivalence, we anticipate that the Division of Clinical Review will review correspondence containing clear, concrete questions related to the planning of a BE study with clinical endpoints, or questions related to adverse events that occur during the conduct of a BE study.

- **Office of Research and Standards**

FDA anticipates that the Office of Research and Standards will review correspondence containing questions, for example, on complex drug products or drug-device combination products.

- **Division of Microbiology**

FDA anticipates that the Division of Microbiology will review correspondence containing inquiries regarding product quality microbiology.

- **Division of Filing Review**

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We anticipate that the Division of Filing Review will review correspondence containing inquiries regarding FDA's Inactive Ingredient Database and drug product formulation.

- Division of Labeling Review

FDA anticipates that the Division of Labeling Review will review, for example, correspondence regarding labeling standards for container/closure systems that are different from the RLD, and appropriate labeling differences.

- Office of Generic Drug Policy

We anticipate that the Office of Generic Drug Policy, which includes the Orange Book staff, will review, for example, correspondence regarding patent listings or RLD questions.

### **V. INFORMATION ON COMMUNICATIONS FROM FDA TO REQUESTORS THAT SUBMIT CONTROLLED CORRESPONDENCE**

For inquiries submitted to [GenericDrugs@fda.hhs.gov](mailto:GenericDrugs@fda.hhs.gov), FDA will provide the following information to a requestor regarding its receipt and consideration of the inquiry.

Upon receipt of a submission, FDA will evaluate whether the submission will be considered a controlled correspondence for the purposes of GDUFA. FDA then will send the requestor one of two emails: (1) an email confirming acceptance of the submission as a controlled correspondence for the purposes of GDUFA, which will include a controlled correspondence tracking number, or (2) an email informing the requestor either that the Agency does not consider the submission a controlled correspondence and the basis for that decision, or that FDA lacks adequate information to make this determination. If a requestor resubmits a request for information that addresses any problem that FDA identified with a previous request, the Agency will consider this a new controlled correspondence and process it as such.

After reviewing the request for information in the controlled correspondence, FDA will respond to controlled correspondence in written form via email to the email address identified in the controlled correspondence. The length and content of FDA's response will depend on the nature of the inquiry submitted. FDA will not respond to status requests regarding pending controlled correspondence.

We recognize that upon receipt of FDA's response to a controlled correspondence, requestors might have follow-up questions or requests for related, additional information. Because Agency staff will have to expend resources to review and respond to these follow-up questions and requests for additional information, FDA will treat the requests as new controlled correspondence. In these instances, we recommend that a requestor submit a new controlled correspondence and include the controlled correspondence tracking number(s) of the previous inquiry to facilitate FDA's review and response.